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Pineal Region Tumors

Nu Thien Nhat Tran

Abstract

The pineal gland is a small endocrine gland located in the brains of vertebrates near the brain center that helps regulate circadian rhythms. Pineal tumors are tumors located in this region including tumors of the pineal gland and tumors of the components and structures of this region. Pineal tumors can compress the third ventricle, squeeze the cerebral drain causing hydrocephalus, compress the brain stem, compress the cerebellum, compress the posterior fossa ... causing various disorders. The pineal gland has a rather complicated anatomy, deep in the brain parenchyma, surrounded by many blood vessels and other important structures, so surgery to approach this area is still a challenge for many surgeons. Because these cancers are so rare, it has always been difficult to collect a large number of cases to study and compare. This chapter will describe the features of pineal tumor from the information collected so far.

Keywords: pineal tumors, pineocyte, Parinaud syndrome, germinomas, teratomas

1. Introduction

The pineal gland is a small endocrine gland located in the brains of vertebrates near the brain center that helps regulate circadian rhythms.

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The pineal gland has a rather complicated anatomy, deep in the brain parenchyma, surrounded by many blood vessels and other important structures, so surgery to approach this area is still a challenge for many surgeons.

Because these cancers are so rare, it has always been difficult to collect a large number of cases to study and compare. This chapter will describe the features of pineal tumors from the information collected so far.

2. Epidemiology

According to many studies, pineal region tumors are rare, accounting for less than 1% of brain tumors in adults, 5–10% in children. In particular, 95% of pineal region tumors are found in patients <35 years old.

Gender distribution of pineal region tumors showed a high incidence in male, with a male: female ratio of 3:1 [1].

Geographically, this tumor is found in many Asian and American people, of which Japan accounts for 16% of the total pineal tumors [2–4]. There is no known reason for this difference.

3. Etiology and screening

Located near the center of the brain, the pineal gland is a tiny organ shaped like a pine cone. It is seen as a mysterious organ because in the endocrine glands, its function is discovered in the end [5, 6]. Researchers claim that it produces and regulates a number of hormones including melatonin. Melatonin (a hormone derived from serotonin) is best known for its role in regulating sleep - maintaining circadian rhythms, and in regulating fertility hormones [7, 8].

Until now, the cause of pineal region tumors has not been clarified. Several studies have noted an association between this tumor and retinoblastoma or rarely with Klinefelter’s syndrome [9, 10]. In addition, no specific genetic mutations have been associated with pineal region tumors.

4. Classification

Tumors of the pineal region have a varied histology that generally can be divided into germ cell and non-germ cell derivatives.

Germ cell tumors are the most common of pineal region tumors. These tumors are classified into two subtypes: germinomas and a group of nongerminomatous germ cell tumors (NGGCTs) which include teratoma, embryonal carcinoma, yolk sac tumor and choriocarcinoma. These tumors arise from pluripotential germ cells, which usually do not reside in the pineal gland. Theoretically, these germ cells mistakenly migrate to the pineal gland during embryogenesis. It’s still not clear why that happened.

The second most common form is pineal parenchymal tumors. Pineal parenchymal cell is a pinocyte. WHO classified it as pineocytoma, pineoblastoma and mixed pineocytoma-pineoblastoma tumors (or PPT of intermediate differentiation).

The pinocyte is surrounded by a stroma of fibrillary astrocytes, which interact with adjoining blood vessels to form part of the blood-pial barrier. These abnormally grown glial cells also become one of the types of pineal region tumors.

Other tumors which located around the pineal gland, are also pineal region tumors. These tumors include papillary tumor of the pineal region, meningioma or metastasis tumor. Papillary tumors of the pineal region are a new classification believed to be derived from specialized ependymocytes. These tumors are so rare that there is very little data available on them.

Germ cell tumors (GCTs)	50% -75%
Pineal parenchymal tumors (PPTs)	14% - 27%
Pineocytoma (14% - 60%)	
PPT of intermediate differentiation (10%)	
Pineoblastoma (45%)	
Gliomas	} 5–26%
Papillary tumors of the pineal region	
Other tumors	

Table 1.
The classification and frequency of pineal region tumors.

The table above shows the classification and frequency of pineal region tumors (Table 1).

5. Diagnostic

Despite their general anatomic location and similar imaging findings, pineal tumors are extremely heterogeneous in histopathology, natural history, and response to treatment. Diagnosis of pineal region tumors is based on clinical manifestations, imaging and pathological results.

Pathological outcomes are the gold standard in diagnosing pineal tumors. However, because the pineal gland is located deep in the brain, so tissue sampling becomes difficult. Consequently, noninvasive diagnosis become useful. Biological markers in serum and cerebrospinal fluid (CSF) provide additional data prior to invasive procedures.

Specific serum and cerebrospinal biological markers combined with clinical evidence and radiographs of pineal mass can guide diagnosis and treatment without the tissue biopsy.

5.1 Clinical presentation

Pineal tumor symptoms usually progress slowly from weeks to years. In the case of rapidly growing tumor may cause acute and severe symptoms [11]. These tumors remain localized to this region where they may compress adjacent structures including the cerebral aqueduct, brain stem, and cerebellum. Signs and symptoms therefore vary and relate to obstructive hydrocephalus, increased intracranial pressure, visual problems, Parinaud syndrome, changes in mental status, and ataxia.

The clinical presentation of these tumors depends on many factors, such as tumor location, its size and extend or patient age. Although the two most common tumor subtypes, GCTs and PPTs, occurred predominantly in children, the third most common, gliomas, were more common in adults. From there, if you encounter pineal region tumors in children, you can think of CGTs or PPTs more than gliomas. The opposite in adults.

One of the most common syndromes is obstructive hydrocephalus. Its presentations are headache (worse in morning), nausea and vomiting. This condition is usually caused by a tumor compressing the Sylvian aqueduct. If left untreated, it may lead to lethargy and death.

Another syndrome is visual problems. Pineal gland is very close to the pretectum so eye symptoms are common. Symptoms of pretectum compression leading to Parinaud's syndrome, which was first described by the French ophthalmologist Henri Parinaud in the late 1800s. This syndrome includes paralysis of vertical gaze, convergence retraction nystagmus, loss of pupillary light reflexes, loss of convergence upper eyelid retraction (Collier's "tucked lid" sign) and "setting sun" sign.

Rarely are symptoms related to the cerebellum. These symptoms include gait abnormality, instability, and frequent falls. The cause is thought to be caused by pressure on the cerebellum from large tumors.

Children with pineal region tumors can present with endocrine malfunction. Some specific endocrine syndromes can arise from secretion of hormones by germ cell tumors. Some of the endocrine disorders that can be mentioned are diabetes insipidus, pseudoprecocious puberty, amenorrhea and growth arrest.

Intracranial hemorrhage is rare but should be considered in pineal adenomas. Firstly, bleeding can cause pineal abscesses or subarachnoid hemorrhage. This

aggravates the symptoms of the disease. Secondly, since this is also one of the complications of surgery, this should be assessed before surgical treatment.

5.2 Imaging

5.2.1 Computer tomography

CT Scan is often used in the emergency, to help diagnose ventricular dilatation caused by pineal region tumor, determine calcification in the tumor and have a role in diagnosing the location, size, density of the tumor [12]. It is worth noting that CT scans are not recommended in children, especially young children. In general, CT Scan is not used to identify or classify pineal tumors.

5.2.2 Cranial magnetic resonance imaging

High-resolution MRI with gadolinium is necessary in the evaluation of pineal region lesions. On MRI, pineal neoplasms appear as solid, lobulated tumors. It allows to clearly identify the location, vascularity, morphology, and structure of the tumor as well as the anatomic relationship with surrounding structures in order to select surgical access routes. Irregular tumor borders may suggest a malignant tumor and surrounding invasion [12].

Although the exact type of tumor cannot be determined, some features can be used to guide a diagnosis. Most germinomas are readily visible on MR, and tend to be of considerable size by the time of presentation. These tumors are isointense on T1-weighted MRI images, are slightly hyperintense on T2, and have strong homogeneous enhancement. Marked contrast enhancement is the rule for germinomas. In addition, in case of suspected germinomas, a MRI of the entire spine is required to assess the metastasis according to cerebrospinal fluid.

Unlike germinomas, teratomas typically have heterogeneous MRI signals. Most have evidence of fat or calcification.

Both pineocytomas and pineoblastomas typically are hypointense to isointense on T1-weighted images, have increased signal on T2, and demonstrate homogeneous enhancement after administration of gadolinium. It is rarely possible to distinguish between pineocytomas and pineoblastomas with MRI.

In addition to MRI, angiography is sometimes used in cases of suspected vascular anomalies.

5.3 Pathology

Tumor cells are removed and sent to a laboratory for examination. This is done to find out the type and grade of the tumor. Since the pineal gland is deep in the brain, there is almost no way to obtain tissue samples without invasive procedures. Consequently, there is usually only a pathological outcome after biopsy or surgery. What's more, not all tumors can perform invasive procedures. In facts., about 11% of biopsies are either undiagnosed or misdiagnosed, showing difficulty in obtaining enough tissue for an accurate diagnosis [13] (**Table 2**).

5.4 Biomarker

Although pineal cells are the only place to secrete melatonin in the body, numerous reports describe an association between melatonin secretion and pineal parenchymal tumors, indicating that very few pineal parenchymal tumors are disturbed melatonin secretion disorders lead to sleep disturbances [15–18]. Therefore,

Tumors of the pineal region	Grade I	Grade II	Grade III	Grade IV
Germ cell tumors		x	x	x
Pineocytoma	x			
Pineal parenchymal tumor of intermediate differentiation	x	x		
Pineoblastoma				x
Gliomas	x	x		x
Papillary tumor of the pineal region	x	x		
Other tumors				

Table 2.
Pathology of tumors of the pineal region [14].

Tumor subtype	Beta Human Chorionic Gonadotropin	Alpha – Fetoprotein	Placental Alkaline Phosphatase
Germinoma	+/-	—	+
Teratoma	—	+	
Choriocarcinoma	+	—	
Embryonal carcinoma	+	+/-	

Table 3.
Biomarkers of germ cell tumors.

melatonin analysis is presently believed to have little clinical use in diagnosing and monitoring response to treatment in pineal parenchymal tumors.

Germ cell tumors are groups capable of increasing the biological markers involved in germ cells. While germinomas and choriocarcinomas can cause an increase in β -hCG, embryonal carcinomas, immature teratomas, and endodermal sinus tumors can cause an elevated alpha-fetoprotein in the serum or CSF. Germinomas are also associated with elevated lactate dehydrogenase and placental alkaline phosphatase.

Biomarkers of germ cell tumors are summarized in **Table 3**.

As described above, these markers can be somewhat helpful for diagnosis, but they are more useful for monitoring response to treatment.

6. Prognosis

Pineal region tumors treatment results depend on the type of tissue, the location and size of the lesion as well as age of patient. In general, patients with germinomas have an excellent prognosis because of the radiosensitivity of these tumors.

A study of incidence, survival and treatment modalities was done based on the SEER data (The Surveillance, Epidemiology, and End Results) on 633 patient diagnosed pineal tumors during the period 1973–2005. The 5-year overall survival (OS) was $65\% \pm 2.1\%$. Among them, the best survival was germ cell tumors (OS = $78.9\% \pm 2.3\%$), followed by glioma (OS = $61\% \pm 9.3\%$) and pineal parenchymal tumors (OS = $47.2\% \pm 4.2\%$) [1].

Recurrent germ cell tumors have been shown to respond to chemotherapy, as have some pineal cell tumors, although to a lesser degree. No conventional approach

is designed for managing recurrence. Chemotherapy, radiotherapy, or radiosurgery can be applied if maximal doses have not already been administered.

7. Treatment

Due to pineal tumor's rarity, there is no consensus to date on optimal treatment. Some suggested that, complete surgical resection is the mainstay therapy for low-grade tumors, whereas a multimodality approach of surgery, radiotherapy, and chemotherapy is the preferred treatment in high-grade tumors. Some other authors encourage that the first treatment for pineal region tumors is surgery, if possible, followed with irradiation and chemotherapy or clinical trials. Clinical trials, with new chemotherapy, targeted therapy, or immunotherapy drugs, may also be available and can be a possible treatment option [13]. So that, treatments are decided by the physician, based on the patient's factors, for example: the age at diagnosis, symptoms, remaining tumor after surgery, tumor type, and tumor location.

Notably, germinomas are exceptional. Germinomas, which are exquisitely radiosensitive, can be cured by conventional radiation therapy alone (40 Gy + 15 Gy boost). Craniospinal radiotherapy is indicated if CFS seeding is found. Therefore, diagnosis of germinomas by MRI and biomarkers becomes particularly important.

7.1 Surgery

The authors support an aggressive surgical approach to pineal region tumors to provide a definitive histological diagnosis. This strategy is based on their surgical experience in 160 operations for pineal region tumors in which operative mortality was 4% with 3% permanent major morbidity.

There are 2 types of surgery corresponding to 2 different purposes.

Firstly, for the treatment of ventricular dilation, there are two commonly mentioned techniques: ventriculoperitoneal shunt and endoscopic third ventriculostomy. Recently an endoscopic third ventriculostomy has been selected. Because this therapy not only drains cerebrospinal fluid but also may take tissue tumor for testing or pathology.

Another therapy is surgery to remove the pineal region tumors. In the past, surgical exploration of the pineal gland was very hazardous. Given recent advances, this surgical approach is typically performed endoscopically using a high-definition operating microscope and stereotactic techniques through a small bony opening at the back of the head, direct approach to these tumors has become relatively safe. The goal of surgery is to obtain tissue to determine the tumor type and to remove as much tumor as possible without causing more symptoms for the person. Evidence suggests that surgical debulking may improve the response to postoperative adjuvant therapy [19].

In summary, patients with hydrocephalus have evidence of pineal region malignancies on MRI may be treated with either third ventriculostomy or ventriculoperitoneal (VP) shunt prior to biopsy or removed.

Complications after surgery cannot be ignored. The most devastating complication of pineal tumor surgery, regardless of the approach, is postoperative hemorrhage. The bleeding can be early or slow for a few days and is often associated with vascular tumors. This is truly a disaster and a great challenge for all surgeons. Some common complications are extraocular movement dysfunction, ataxia, altered mental status as well as seizures, or hemiparesis. Some factors increased incidence of surgical complications include prior radiation treatment, severe preoperative neurologic symptoms, malignant tumor pathology, and invasive tumor characteristics.

7.2 Radiotherapy

Depending on each case, it is possible to have postoperative radiotherapy, concurrent postoperative chemotherapy, or only radiation therapy. There are a number of projection fields that can be applied, for example: whole brain (for multifocal metastatic cancers), tumor region and tumor margins (for large tumors that cannot be removed). The dose of radiation therapy depends on the type of histopathology, tumor location, age, physical condition, malignancy. Some potential complications of radiation therapy are hypothalamic and endocrine dysfunction, cerebral necrosis, dementia. They need careful evaluation and monitoring.

As mentioned above, germinomas are among the most radiosensitive tumors, therefore these tumors can be cured by conventional radiation therapy alone [20]. However, these patients should be carefully monitored with serial MRI to evaluate tumor recurrence or progression.

Remember, radiation therapy is only available for children 5 years of age and older. It has been noted that even low radiation doses can have significant long-term effects on children's cognitive development.

7.3 Systemic therapy

Chemotherapy is a supportive treatment that enhances the effectiveness of surgery and radiation therapy [21, 22]. Treatment regimens have included various combinations of vincristine, lomustine, cisplatin, etoposide, cyclophosphamide, actinomycin D, and methotrexate.

Chemotherapy is usually given after surgery, after, or simultaneously with radiation therapy. Using chemotherapy as the first step in the treatment of pineal tumors has only been shown to be effective in certain cases. The success of radiotherapy in the treatment of germ tumors has discouraged the use of chemotherapy as the primary treatment. Chemotherapy should be considered the first line of treatment in young children, especially children younger than 5 years.

8. Follow up

After treatment for pineal tumors there are many chronic health problems to be aware of and to screen for in long-term survivors. Lifelong follow-up of children with pineal region tumors is required. MRI scans and biomarkers should be obtained on a periodic basis, even if the result were not abnormal. Patients should be evaluated by an endocrinologist and ophthalmologist every 1–2 years.

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